REMARKS

Upon entry of the above amendment, claims 1-13, 15 and 18-20 will be pending in the present application. Applicants respectfully submit that the amendments to the claims do not add any new matter within the meaning of 35 USC §132.

1. Rejection of claims 18-20 under 35 U.S.C. §112, 1st paragraph

The Official Action states that claims 18-20 are rejected under 35 U.S.C. §112, 1st paragraph "as failing to comply with the enablement requirement." The Official Action also states, in relevant part:

> The specification generally mentions hundreds of different disease conditions on pages 55-56 which can be treated by the PDE4 inhibitors. However, there is no teaching either in the specification or the prior art references provided showing well established utility of PDE4 inhibitors in all of these disease conditions.

RESPONSE

Applicants respectfully traverse this rejection. However, solely to expedite the prosecution of this application, applicants have introduced an amendment to both claims 18 and 19 and have filed herewith several references in an Information Disclosure Statement which provide enablement for the specifically recited diseases.

In particular, applicants have amended claims 18 and 19 to recite specific diseases. Applicants have amended claim 18 to recite "asthma, COPD, allergic rhinitis, rheumatoid arthritis, dermatoses, ulcerative colitis or Crohn's disease". Claim 19 recites "asthma and/or COPD". Specific basis may be found for these amendments on page 55, 2nd paragraph.

In order to demonstrate enablement for these diseases, applicants submit herewith an Information Disclosure Statement citing four (4) references. Each reference is discussed below with reference to its demonstration of enablement of the particular disease.

Souness et al. : Asthma, COPD, Rheumatoid Arthritis and Dermatoses

The Souness et al. reference demonstrates enablement for the treatment of asthma, COPD, rheumatoid arthritis and dermatoses (such as atopic dermatitis) by administering a PDE4 inhibitor. In particular, Table 6 (page 144) shows that the selective PDE4 inhibitors Tibenalast, Piclamilast (RP73401), Arofylline (LAS-31025), CDP-840, Ariflo (SB 207499) and Atizoram (CP-80633) were undergoing clinical trials for the treatment of asthma.

In addition, the selective PDE4 inhibitor Ariflo (SB 207499) was undergoing a clinical trial for the treatment of COPD. Souness et al. go on to state at page 150, 3rd paragraph, that "[t]he most exciting development has been the demonstration of efficacy by Ariflo in phase II/III clinical trials in COPD patients".

Further, Table 6 shows that the selective PDE4 inhibitor Piclamilast (RP73401) was undergoing a clinical trial for the treatment of arthritis. On page 146, in section 8, entitled "Potential of PDE4 inhibitors in arthritis", Souness et al. teach that "RA patients treated with piclamilast…in a small clinical study showed a positive trend in respect of serum concentrations of IL-6 and CRP although the corresponding levels of TNF-alpha and IL-1 were unaffected. Patients reported some improvement in symptoms."

With regards to the dermatoses indication, Souness et al. teach that the selective PDE4 inhibitor Atizoram (CP-80633) was being clinically studied for its effects in the treatment of atopic dermatitis. In particular, Souness et al. teach on page 148, section 10, entitled "Potential of PDE4 inhibitors in dermatological disorders", that PDE4 inhibiting "compounds have been evaluated with some success in patients with dermatological complaints such as atopic dermatitis (AD) and psoriasis." Souness et al., in section 8.2, also teach "Ro 20-1724 and CP-80633 demonstrate some efficacy when applied topically to AD patients. For example, atizoram, when applied as a topical ointment (0.5%) over 28 days to affected areas in 20 AD patients, demonstrated efficacy with significant reductions in all inflammatory parameters measured."

Accordingly, the Souness et al. reference demonstrates that a person of ordinary skill in the art would be enabled to practice

the presently claimed methods as they relate to asthma, COPD, rheumatoid arthritis and dermatoses.

Montana et al. : Asthma, COPD, Rheumatoid Arthritis, Crohn's Disease and Dermatoses

The Montana et al. reference demonstrates enablement for the treatment of asthma, COPD, rheumatoid arthritis, Crohn's disease and dermatoses by administering a PDE4 inhibitor.

With regards to asthma, Montana et al. state in Table 1 (page 42) that the PDE4 inhibitors Arofylline, Cilomilast, Roflumilast, V-11294A, BAY-19-8004, SCH-351591 and PD 189659 were in various stages of clinical study for their effect in the treatment of asthma. Further, Montana et al. go on to state on page 45, 1st paragraph of text, that "[t]he efficacy of PDE4 inhibitors in animal models of asthma and COPD are well documented. A large number of structurally diverse, selective PDE4 inhibitors have demonstrated their ability to inhibit bronchoconstriction and airway hyper-responsiveness, eosinophil infiltration and local cytokine recruitment in a variety of models involving a range of stimuli."

With regards to COPD, Montana et al. state in Table 1 that the PDE4 inhibitors Cilomilast, Roflumilast and BAY 19-8004 were in either Phase II or Phase III development for the treatment of COPD.

With regards to rheumatoid arthritis, Montana et al. state on page 46 that "[*i*]*n vitro* and *in vivo* evidence suggesting that PDE4

inhibitors would be expected to be beneficial in the treatment of rheumatoid arthritis has been summarized recently (9,45). PDE4 inhibitors have been found to be efficacious in several animal models of arthritis (45)."

With regards to Crohn's disease, Montana et al. teach in Table 1 that the PDE4 Inhibitor CDC-801 by Celgene was in Phase II clinical trials for the treatment of Crohn's disease.

With regards to dermatoses, Montana et al. teach on pages 45-46 that "[t]he rationale for the use of PDE4 inhibitors in the treatment of atopic dermatitis and psoriasis has been discussed". Montana et al. go on to state that the selective PDE4 inhibitor "Arofylline was as effective as prednisone in controlling pruritis and was also effective in controlling skin lesions."

Accordingly, the Montana et al. reference demonstrates that a person of ordinary skill in the art would be enabled to practice the presently claimed methods as they relate to asthma, COPD, rheumatoid arthritis, Crohn's disease and dermatoses.

Schmidt et al. : Allergic Rhinitis

The Schmidt et al. reference demonstrates enablement for the treatment of allergic rhinitis by administering a PDE4 inhibitor.

In particular, the Conclusion contained in the abstract of page 530 states that "a PDE4 inhibitor, roflumilast, effectively controls symptoms of allergic rhinitis. Thus, PDE4 inhibitors might be a future treatment option not only in allergic asthma but

also in allergic rhinitis or the combination of the 2 diseases."

Accordingly, the Schmidt et al. reference demonstrates that a person of ordinary skill in the art would be enabled to practice the presently claimed methods as they relate to allergic rhinitis.

Dyke et al. : Ulcerative colitis

The Dyke et al. reference demonstrates enablement for the treatment of ulcerative colitis by administering a PDE4 inhibitor. In particular, on page 7, Dyke et al. state that "[i]n a dextran sulfate induced model of colitis in the rat, oral administration of rolipram...and arofylline...resulted in amelioration of bleeding and a reduction in inflammatory markers. Rolipram has also been shown to be efficacious in the TNBS colitis model in rats, ameliorating the course of disease and preventing late collagen deposition." "Suppression of colonic TNF-α concentrations was also observed."

Accordingly, the Dyke et al. reference demonstrates that a person of ordinary skill in the art would be enabled to practice the presently claimed methods as they relate to ulcerative colitis.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 18-20.

2. Rejection of claims 1-5 and 18-20 under 35 U.S.C. §112, 2nd paragraph

The Official Action states that claims 1-5 and 18-20 stand rejected under 35 U.S.C. §112, 2nd paragraph as being indefinite.

In particular, the Official Action states, in relevant part:

> Claims 1-5, the values of variables R1, R2, R4, R6 and R7 defined as -----completely or predominantly fluorine substituted ------ is vague, confusing and indefinite.
>
> In claim 2, the value of variable R5 defined as -----1-4C-alkyl2----- is indefinite since its meaning is not clear and furthermore, lacks antecedal basis.
>
> In claim 2, the value of variable R6 defined as ----1-4C-alkoxy---- is mentioned twice. Should it be 1-4C-alkyl at first occurance to be consistent with claim 1?
>
> In claim 18, the specific illnesses treatable by PDE inhibitor are not defined.
>
> In claim 19, specific airway disorders are not defined.
>
> In claim 20, specific skin diseases are not defined.

RESPONSE

Applicants respectfully traverse the rejections of claims 1-5 and 18-20.

With regards to the rejection of claims 1-5, applicant respectfully submits that the phrase "completely or predominantly fluorine-substituted" is clearly defined at page 3 in paragraphs 1 and 2. The last sentence of each of these paragraphs states that "'Predominantly' in this connection means that more than half of the hydrogen atoms of the [substituent] radicals are replaced by fluorine atoms." Accordingly, a person of ordinary skill in the art would understand this phrase and, as such, it is not indefinite.

With regards to the rejection of claim 2, applicants

respectfully submit that claim 2 has been amended to correct the clerical errors. In particular, "1-4C-alkyl2" has been deleted and has been replaced with "1-4C-alkyl". Also, one of the recitations of "1-4C-alkoxy" has been amended to recite "1-4C-alkyl" to be consistent with claim 1.

With regards to the rejection of claims 18-19, applicants respectfully submit that specific diseases are now recited in these claims.

With regards to the rejection of claim 20, applicants respectfully point the Examiner's attention to page 55, 2nd paragraph of the specification wherein the term dermatoses is discussed. In particular, the specification states that dermatoses includes such diseases as psoriasis, eczema, pruritis and acne, among others. As such, a person of ordinary skill in the art would understand the term dermatoses and, as such, it is not indefinite.

Accordingly, applicants respectfully request that the rejection of claims 1-5 and 18-20 be reconsidered and withdrawn.

3. Allowable subject matter

The Official Action states that claims 6-13 and 15 are objected to, but would be allowable if rewritten in independent format.

RESPONSE

Applicants thank the Examiner for this indication of allowable subject matter. However, this objection is moot in view of

applicants' remarks and amendments which have overcome the rejection of the base claims.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this objection to claims 6-13 and 15.

CONCLUSION

Based upon the evidence and amendments submitted herewith and the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the objection and rejection and allow pending claims 1-13, 15 and 18-20. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if he has any questions or comments.

Respectfully submitted,
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